ANNUAL REPORT

OF

THE HOWE LABORATORY OF OPHTHALMOLOGY

HARVARD MEDICAL SCHOOL

AT THE

MASSACHUSETTS EYE AND EAR INFIRMARY

1965

243 CHARLES STREET
BOSTON, MASSACHUSETTS

STAFF

David G. Cogan, M.D.: *Henry Willard Williams Professor of Ophthalmology – Director*
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Selma Hayman, Ph.D.*: *Research Fellow in Ophthalmology*
Lorenzo O. Merola, B.S.: *Technical Associate*
Charles Snyder: *Librarian*

TEMPORARILY ATTACHED TO THE LABORATORY

Special Fellowships:

Jack E. Goldstein, M.D.* *USPHS*
Robert S. Hepler, M.D.: *USPHS*
Ivar Hørven, M.D.: *USPHS (International)*
Arnold J. Kroll, M.D.: *University of Miami*
John A. Stanley, M.D.: *USPHS*

Residents of the Massachusetts Eye and Ear Infirmary:

Richard F. Brubaker, M.D.
William J. Collis, M.D.
Stephen J. Fricker, M.D.
Robert A. Gorn, M.D.
Howard Leibowitz, M.D.
Joseph Michon, Jr., M.D.
Anthony B. Nesburn, M.D.
Ronald C. Pruett, M.D.
Richard A. Thoft, M.D.
David M. Worthen, M.D.

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* Transferred to another institution during 1965.

Ever since assuming the ritual of writing Annual Reports, some twenty years ago, we have accented growth or the need for growth. From a few rooms with a staff of a half dozen investigators we now have a full floor committed to research and our staff is several fold that of two decades ago. Our budget has risen to heights that would have seemed incredible then. The theme has been growth because that is the conventional sign of progress and because that has presented our most pressing problems.

Yet we fear that the things we have emphasized, at least the tangible things, will be interpreted as our idea of real growth. We have no such illusion. The really important things are less obvious. They comprise contributions to the background of knowledge, influence on potential investigators or practitioners, and stimulation of students and associates, but all these are as difficult to represent in an Annual Report as they are elusive to evaluate in precise terms.

A growth-related question which we have often pondered is: How large should an eye research laboratory be? We have no pat answer but we do know that the problems in the science of ophthalmology and in ophthalmic disease are immeasurably great. So long as we have investigators with the competence and enthusiasm to devote their lives to dispelling our ignorance and so long as we have benefactors willing to provide reasonable means of support, we believe there should be no arbitrary limit placed on growth. It is when the two get out of balance that we have cause for worry. We have only small-sized worries and we continue to grow.

RESEARCH ACTIVITIES

Glaucoma and Intraocular Fluid Dynamics

For many years research on glaucoma has been closely allied in our institution to the clinical problems of glaucoma. For at least 25 years Dr. Paul Chandler has been chief mentor in this field. He has been largely responsible for the development of the Glaucoma Consultation Service as an outgrowth of the Howe Laboratory, and almost daily he has come to the laboratory to confer with Dr. Grant on problems of glaucoma. Out of these conferences has come a book by Drs. Chandler and Grant recording the clinical concepts and practices which have developed during these years.

The book, "Lectures on Glaucoma," provides practical advice to students and practitioners of ophthalmology on the recognition and management of glaucoma in its various forms, both in adults and in children. It should be regarded as a sort of progress report, since both authors confidently believe that research on glaucoma will surely, before long, bring further clarification of the fundamental concepts and improvement in the treatment.

In the clinical research on glaucoma carried out under Dr. Grant's supervision, an important part is performed by postgraduate research fellows attached to the Glaucoma Consultation Service. During the first half of this year this position was held by Dr. Roland E. Houle, and during the second half by Dr. Thomas Hutchinson. One of the subjects under continuing investigation has been the lowering of the pressure in the eyes of glaucomatous patients by alcohol. The purpose of this study has been to learn more about fundamental mechanisms of control of intraocular pressure, rather than to consider alcohol as a therapeutic agent. Dr. Houle has confirmed that a single oral dose of alcohol can lower the pressure for several hours, as reported by Dr. Peczon in last year's report. Going further, with the help of patients who volunteered their cooperation in these studies, Dr. Houle has now determined that continuing administration of alcohol for a longer period can extend the duration of pressure-lowering even beyond the duration of the diuretic effect of the alcohol.

One of the mechanisms which Dr. Houle has had under consideration to explain the lowering of pressure implicates a selective and well-recognized suppressant effect of alcohol on the anti-diuretic hormone of the pituitary, which may induce general dehydration. In support of this possibility, Dr. Houle has found that the influence of alcohol on the intraocular pressure in glaucoma can be partially blocked by administering an extra supply of the anti-diuretic hormone. As a corollary to this observation, he has also been examining the response of intraocular pressure to alcohol in patients who have a pathologic deficiency of this hormone, but these studies are not yet complete.

Dr. Houle has also attempted to ascertain whether alcohol may exert its pressure-lowering influence by an action directly on the eye, but solutions of alcohol as strong as the eye can tolerate on its outer surface have caused no decrease in pressure.

Ophthalmic residents of the Infirmary occasionally take advantage of an opportunity to carry out some clinical research during their assignment to the Glaucoma Consultation Service while learning proper care of glaucomatous patients. Dr. Ernst Meyer in this capacity has evaluated the influence of a contraceptive hormone pill, known as Enovid, on the intraocular pressure in glaucoma, and has found it to have a usefully beneficial effect. Dr. Meyer undertook the evaluation on the basis of knowledge that the intraocular pressure is influenced by pregnancy, by phases of the menstrual cycle, and by certain of the sex hormones which have been administered experimentally. His results in the study of the commercial hormone pill which is now in very widespread use have two main points of practical significance: one is to relieve patients and their physicians of concern regarding possible unwanted effects of the pill in the presence of glaucoma; the other is to bring attention to a potential additional means for treating glaucoma in patients who are not responding adequately to the standard antiglaucoma medications.

In the laboratory, Dr. Brubaker, in association with Dr. Kupfer, has investigated what is known as pseudofacility. Pseudofacility has been defined as the decrease in net inflow into the eye which occurs when the intraocular pressure is elevated. Dr. Brubaker has indirectly evaluated pseudofacility in rhesus monkeys under deep anesthesia by means of quantitative aqueous perfusion of the eyes with and without artificial elevation of the pressure in the venous circulation of the head. Pseudofacility has been calculated from the relationship between two steady-state conditions. In these circumstances it constituted approximately one-third of the total. This is a step toward evaluated pseudofacility in man. The next step experimentally may be to see what effect drugs such as pilocarpine and acetzolamide may have on it.

Histopathology

Study of the normal and pathological retina continues to be one of the prime interests of Dr. Kuwabara and Dr. Cogan. The pathogenesis of diabetic retinopathy has been found to be associated with a specific vulnerability of mural cells in the capillaries and thereby formation of shunt vessels. The senile and ischemic vascular changes, on the other hand, have been found to be associated with preferential loss of endothelial cells. Initially the nuclei disappear while the cytoplasm remains intact. Later when the endothelium disappears entirely, the capillary lumina become filled by an ingrowth of Müller cells. These age-related changes in the retina were presented by Dr. Kuwabara this past year in a Symposium on Vascular Disorders of the Eye held at San Francisco.

New methods of tissue fixation for electron microscopy, especially the use of glutaraldehyde, have permitted better identification of Müller cells and recognition of ultrastructural details in the retinal neurones. Dr. Kuwabara is embarked on a long-term study of the relationship between these glial and nervous cells of the retina and of their anatomic connections at the synapses.

With the improved technique of electron microscopy, a new component, the microtubule, has been found to be abundantly present in retinal neurones. The tubules, measuring approximately 200 A° in diameter, form fascicles that constitute much of the bulk of the neuronal processes. In the paranuclear region they either disappear or become less regularly arranged. The function of these microtubules is not known but their morphology is now clear. A preliminary report of the findings was presented by Dr. Kuwabara at the 8th International Congress of Anatomists in Wiesbaden, Germany.

The cornea has also been subjected to combined studies by electron and light microscopy with special emphasis on wound healing. The corneal ground substance, heretofore believed to be a homogenous, amorphous fluid, was found to contain many fine fibrils continuous with the stromal cells. The amount and distribution of these fibrils varied greatly after injury or other deviations from the normal. The epithelial sliding phenomenon which follows corneal abrasions and serves importantly in corneal wound healing was subjected to various enzyme poisons. Only iodoacetate caused a significant inhibition.

The fine structure of uveal melanoma cells has now been examined electron microscopically in a series of 12 cases by Dr. Kroll with the aim of detecting degrees of malignancy. The cells of the more benign tumors showed attachments to each other by desmosomes and contained predominantly free ribosomes within their cytoplasm, whereas the cells of the more malignant tumors showed no intercellular attachments and contained ribosomes that were free and ribosomes that were bound to membranes.

Other investigations correlating light and electron microscopy include: ocular muscles in the normal and dysthyroid state (Dr. Kroll); microanatomy of iris innervation (Dr. Worthen); and movement of tracers across cell barriers in the eye and in the central nervous system (Drs. Kuwabara and Worthen). In addition Dr. Hørven, an International Fellow from the University of Oslo, has continued his studies on exfoliation of the lens capsule.

The interesting ocular effects of 1, 2 dichlorethane were investigated by Dr. Quevedo in conjunction with Dr. Kuwabara. This substance, variously used in the past as an anesthetic and lacquer solvent, has intrigued toxicologists and ophthalmic pathologists since it was found more than half a century ago to induce necrosis of corneal endothelium in dogs after inhalation. Foxes and other canine animals were also reported to develop corneal opacification after inhaling it but non-canine animals were allegedly unaffected. Dr. Quevedo found he could repeat the observation on dogs readily by intramuscular injection of the compound. Flat mounts of the corneal endothelium showed vacuolization as early as 3 hours after the injection and gross metamorphosis of the cells in 12 hours. Healing began in 24 hours and was complete at 54 hours. Cats showed a similar necrosis of the endothelium but, unlike the dogs, they did not develop corneal opacity. With excessive doses the animals developed symptoms of central nervous system origin (ataxia and convulsions) and were found at necropsy to have extensive liver necrosis.

An entity which we have chosen to call Microcystic Dystrophy of the Corneal Epithelium was described for the first time this past year. Drs. Cogan, Donaldson, Kuwabara, and Dr. Don Marshall (Kalamazoo, Michigan) collaborated on a clinical and histological study of this condition which presents as discrete and evanescent opacities in the corneal epithelium. Microscopic examination showed the opacities to consist of tiny cysts containing cellular debris which is intermittently discharged onto the surface of the cornea.

Biochemistry

Galactose cataracts have been Dr. Kinoshita's model for sugar cataracts and the experimental analogs of diabetic cataracts in human beings. Out of these studies has come the sugar-alcohol, osmotic hypothesis of cataractogenesis. This past year Dr. Kinoshita, Dr. Hayman, and Mr. Merola have resolved some biochemical changes in the early stages but much further study is necessary to account for the changes in the later stages.

The cataracts are produced either in life by feeding galactose to rats or in the test tube by culturing rabbit lenses in a high galactose medium. The galactose-alcohol, dulcitol, accumulates maximally in the epithelium where the enzymes necessary for dulcitol formation are chiefly present. With the osmotic imbalance the amino acid and potassium transport mechanisms, which others have found to occur in the epithelium, become altered as cataracts mature.

Studies on protein synthesis in the lens have been carried out by Drs. Spector and Kinoshita. It is generally accepted that in animal tissues DNA-dependent-messenger-RNA synthesis must be maintained for the continued production of protein. The study on the lens has shown that actinomycin D, an antibiotic which inhibits DNA-dependent-RNA synthesis, virtually stops this type of synthesis within four hours after the lens is exposed to it. However, after 30 hours in the presence of actinomycin a significant extent of protein synthesis resumes. In contrast to other tissues, therefore, the lens contains a messenger RNA which is unusually stable. Furthermore, the findings suggest that when the nucleus and consequently the DNA is lost from a lens fiber the presence of a stable messenger RNA permits the continuation of protein synthesis.

Dr. Spector has proceeded a step further in the elucidation of the protein synthetic mechanism of the lens. He has successfully isolated polyribosomes from calf lens by centrifugation in a sucrose-density gradient. These polyribosomes are the site of protein synthesis in the lens. Dr. Spector and Dr. Dorothy Travis (Orthopedic Research at the Massachusetts General Hospital) have shown by electron microscopy that these RNA particles are composed of a number of ribosomes strung together by long strands of messenger RNA. These strands average 12,000 A° in length. From the length of the messenger RNA, it is possible to estimate the size of protein synthesized. It appears that these ribosomes are capable of synthesizing proteins with a molecular weight of 57,000. This is approximately the size of subunits of lens proteins determined by Dr. Spector and others.

The clinical impression that some of the anticholinesterase drugs, used widely in the treatment of glaucoma, may cause cataracts has stimulated us to investigate the possible biochemical relationships. By means of a spectrophotometric technique, Dr. Michon has found a cholinesterase which seems limited to the surface membranes of the lens. Further localization is being attempted histochemically. Preliminary studies have indicated that the rabbit lens will become opaque with high doses of demecarium bromide (Humorsol) and that electrolyte imbalances in water and cation exchanges occur with lower doses in the presence of clear lenses.

In the retina the major event of interest to the biochemist concerned with visual mechanisms is the conversion of vitamin A to the photosensitive pigments. One step in this process is the esterification of vitamin A by fatty acids. The metabolic origin of these fatty acids is not yet known but Dr. Futterman has found an active fatty acid synthesizing enzyme system in the supernatant fluid fraction of the tissue. This efficiently converts two of the six carbon atoms of citric acid to long chain fatty acid (laurate, 6%; myritate, 30%; palmitate, 60%; stearate, 4%). Other supplements which have to be supplied for fatty acid synthesis include manganous ion, bicarbonate, isocitrate, coenzyme A, TPN and ATP. An apparently independent fatty acid synthesizing system is present in the retinal microsomes and is now being studied.

Further information on the metabolism of vitamin A in the visual process is being explored by Dr. Gorn. The turnover of retinene in vitamin A deficient rats is being altered by various antimetabolites and the effect on vision recorded by electroretinography.

Continuing a long term interest in fat metabolism in the cornea, Dr. Andrews has been able to demonstrate synthesis of cholesterol and of fatty acid from glucose by cells of the cornea. This appears to be effected by the cell microsomes and is believed to serve for metabolic turnover in cell membrane repair.

Neuro-ophthalmology and Neurophysiology

The visual pathways present an open challenge for the application of medical electronics provided one has the requisite sophistication in the fields of ophthalmology and engineering. Dr. Fricker has such qualifications and has utilized them to design and assemble the equipment for detecting signals in the eye and in the brain resulting from flashes of light. The crucial instrument is a "Synchronous Detector" which measures the amplitude and phase angle and thereby the delay time of the electric impulse. Such measurements may reveal information of diagnostic significance. Preliminary observation on a series of normal persons and on patients with lesions of the visual pathways are promising.

The ocular signals reflect the function of the entire retina whereas the signals reaching the brain reflect predominantly the function of the macula. The ocular signals are age-independent whereas the occipital signals show regular changes with age. Opacities of the ocular media do not impose a significant hindrance to this type of measurement so that we may have an objective means of estimating macular function in patients with cataracts or corneal opacities which prevent the usual methods of macular evaluation. The method may also be employed in evaluating the visual function of infants and animals where objective testing is required. But since this is a relatively new method of examination, its calibration will require laborious and cautious interpretation of a large number of subjects.

Of the many neuro-ophthalmic problems with which we have had contact in the past few years, one of the most interesting has been unilateral internuclear ophthalmoplegia. Whereas bilateral internuclear ophthalmoplegia is a common manifestation of multiple sclerosis, we have found that the unilateral variety almost always points to a vascular lesion. This observation received further confirmation this past year by the clinicopathologic study of a case by Drs. Kupfer and Cogan. Serial sections of the brain stem revealed a circumscribed infarct of one medial longitudinal fasciculus homolateral to the side of the paralysis and just posterior to the third nerve nucleus.

Another unique opportunity presented this past year to study a condition which had not been previously known to have ocular manifestations. The condition, called Farber's lipogranulomatosis, is a metabolic and so far invariably fatal disease of infants characterized by nodular masses of glycolipid overlying the joints, on the larynx and in various other tissues of the body. The patient whom we had an opportunity to study had perifoveal opacities somewhat similar to the "cherry-red" spot of Tay-Sachs disease. Histochemical investigation revealed a birefringent glycolipid in the ganglion cells that dissolved in most organic solvents but was not sudanophilic. This disease provides another instance in which the eye constitutes a site where the nature of a metabolic by-product is uniquely accessible for observation and identification.

A neuro-ophthalmic entity to which we may have made a small contribution this past year is myasthenia gravis. This disease has the dubious distinction of being one of the most missed diagnoses in neuro-ophthalmology so that any sign alerting the clinician to the diagnosis has considerable value. One hitherto unreported sign is what we have called the "twitch reaction." This may be manifest in movements of the lid and, occasionally, of the eye. In the former case it consists of momentary elevation of a ptotic lid on directing the gaze from a position of infraversion to the straight-ahead position. In the case of eye movements the twitch reaction consists of momentary jelly-like oscillations of the eye on changes of fixation. The twitch reaction is a frequent and highly characteristic manifestation of myasthenia. It was described this past year, together with a moving picture demonstration, by Dr. Cogan in an address to the Japanese Ophthalmological Society.

In comparing the retinal blood pressures in the two eyes as part of a neuro-ophthalmic evaluation we have occasionally been called upon to assess the pressure in patients with glaucoma. What effect, if any, does inequality of the intraocular pressure have on the retinal blood pressure measurements? Drs. Goldstein, Peczon, and Cogan examined this question in twelve patients with unequal intraocular pressures making measurements before and after equalizing the pressure in the two eyes. It appears that an elevated intraocular pressure gives an erroneously low reading of the diastolic blood pressure and must be taken into account in ophthalmodynamometry of patients with glaucoma. The systolic pressure, however, is unaffected.

In their studies of the lateral geniculate body, Drs. Kupfer and Jack Downer (University College, London) have found a regular decrease in metabolic activity of this visual relay after interruption of the optic tract. This decrease begins about the fifth day after denervation. To their surprise they also found a burst of metabolic activity, evidenced by increased glucose oxidation, amino acid incorporation and DPNH-diaphorase enzyme activity, in the first 24 hour period and an increase in the ribonucleic acid in the denervated geniculate neurones. These observations point to specific interactions of the optic nerve with the first processing station for visual information in the central nervous system. The initial change is now being further explored by electrophysiological and pharmacological means.

Immunology and Virology

The failure of some corneal transplants to remain clear is now recognized to be an immunologic rejection similar to that underlying the failure of transplants in other organs. From a research point of view the process in the cornea is particularly advantageous to study because of its accessibility for experimental observation and quantification. In last year's Report we noted that Drs. Leibowitz and Elliott had successfully prevented the rejection reaction in animals by intramuscular injection of the antimetabolite, 6-mercaptopurine, but this was effective only in doses that produced serious side effects. Experiments with a chemically related drug, Imuran, were similarly successful in suppressing the rejection reaction but this drug was also impractically toxic for prolonged use in the doses necessary to maintain clear corneas. Currently, laboratory investigations are being directed toward combining short-term administration of Imuran with long-term treatment by corticosteroids.

Whereas the foregoing studies have the very practical purpose of obtaining clear corneal grafts, a more basic study is in progress on some of the pathogenetic factors in the immunologic reaction. Drs. Elliott and Leibowitz have induced standard immunogenic reactions in the cornea, and together with Dr. Martin Flax (Pathology Department, Massachusetts General Hospital), they have investigated the nature of the cellular infiltrate and of the immunologically competent cells at various time intervals after the sensitization. The aim is to identify the cells in the allergenic response and to differentiate them from other reactive cells in the inflammatory response.

A number of problems relating to ocular virology have been explored by Dr. Nesburn during his year of preclinical research and may be continued at the Infirmary if space can be found for a research laboratory on microbiology. The possibly virologic bases for several obscure ocular diseases were specifically investigated and the factors underlying the reactivation of herpetic keratitis were studied experimentally. Although the results are preliminary and not yet reportable, we are confident that this most recent adventure in microbiology will be productive. One needs only to recall that a similiar undertaking a few years ago led to the discovery of the practical usefulness of IDU for herpetic keratitis.

Instrumentation

Clinical photography has long been an important adjunct to the Laboratory's research and teaching functions and Dr. Donaldson's pioneering has led the field in three-dimensional, close-up photography of the anterior segments of the eye. Dr. Donaldson has now perfected a camera for stereoscopic photography of the fundus using a single flash exposure and a unique method for binocular focussing. This is the first camera which will take the two pictures of the stereoscopic pair simultaneously and obtain consistently good fundus photographs. With it Dr. Donaldson is assembling a series of stereoscopic illustrations of clinical conditions and hopes to have a photographic collection depicting the back of the eye that will parallel the collection he has accumulated over the years for the front of the eye.

Another recent development is the construction of an instrument for the measurement of corneal thickness. Based on the split-ocular principle used in heliometers, this apparatus is attached to the standard biomicroscope and permits measurements with an accuracy of 1.3%. It can be used for either clear or cloudy corneas and should be useful in evaluating corneal disease.

Under trial is a binocular hand ophthalmoscope that permits direct viewing of the fundus stereoscopically. This ophthalmoscope has the advantage over indirect ophthalmoscopes of being simpler for those accustomed to the direct method and of permitting greater magnification of the image. It has, however, definite limitations for examination of the fundus periphery.

One further instrument developed by Dr. Donaldson is a headlamp-magnifying-loop with light attached for examination of otherwise inaccessible cavities. This instrument provides an illumination that is practically co-axial with the viewing system. To date this new headlamp has been found most useful in the repair of blow-out fractures of the orbital floor where the surgery involves visualizing a relatively inaccessible area.

A possible improvement in surgical removal of cataracts is suggested by a new cryoextraction probe developed by Drs. Brubaker and Worthen. Cryoextraction is currently a popular method of cataract removal by which the lens is made to adhere to an applicator through freezing. Several instruments have been described. The present one has the advantages of being small, light, and inexpensive. Its usefulness is being currently evaluated at the Infirmary.

TEACHING AND TRAINING

While the primary function of the Howe Laboratory is research, teaching functions are an indissociable part of it. There is, in fact, no clear separation between the two. The Laboratory staff participates heavily in Harvard's postgraduate course on the basic sciences in ophthalmology, and to some extent in the undergraduate courses. But its greatest influence is at the individual level. About half the resident staff of the Infirmary spend one or more years in the Laboratory learning the techniques and critiques of research. In the summer months a few medical students and college students learn methods in ophthalmic biology and some return in subsequent years to participate in research projects.

A host of visitors come to the Laboratory each year, mostly travelers who stop only a day or so but many have remained for several weeks to study Dr. Donaldson's photographic collection or to learn Dr. Kuwabara's technique of retinal digest preparations. One visiting department head spent several weeks to gain experience before setting up a research facility in his own department. Another visitor, Dr. Hørven, from the University of Oslo is spending a year as an International Fellow in research and observation. Our doors are always open although the space inside is far from adequate.

Ophthalmology's first venture into programmed instruction was formalized this past year with a text on refraction prepared by Drs. Reinecke and Herm. The initial reaction to this form of teaching as tried out in several postgraduate courses has pointed up definite advantages. A similar text on strabismus is in preparation.

ORGANIZATION AND SERVICE FUNCTIONS

Growth in the coming year will require continuing adjustments. We have not yet succeeded in acquiring the additional space which we so urgently need. Yet we have grown to the point of bursting, and several of our staff are leaving or have left. Three are taking on the roles of department chairmen and three division heads. Dr. Friedman has become department chairman at Boston University. Dr. Kupfer will be department chairman at the University of Washington and Dr. Elliott department chairman at Vanderbilt University. Drs. Spector, Futterman, and Andrews will be in charge of the biochemistry divisions at Columbia University, the University of Washington, and Vanderbilt University, respectively. Dr. Richard Robb who has just finished his Laboratory-Infirmary traineeship is heading up the newly activated Department of Ophthalmology at Boston's Children's Hospital Medical Center. Like the parent who faces the inevitable disruption of the family, we have mixed feelings. We take just pride in the offsprings' accomplishments but have concern for the necessary reorganization of the home.

A substantial Center Grant has been awarded the Infirmary by the Public Health Service for development and integration of its clinical research in ophthalmology. Although this affects only a small part of the Laboratory directly it will have considerable indirect effect. The Center Grant will support much of Dr. Donaldson's activities and, it is hoped, relieve the Laboratory of some of its budgetary responsibilities in the strictly clinical sphere.

Under discussion but far from settled as yet is the possibility of establishing a Vision Information Center in conjunction with the Howe Library and Harvard's Countway Library. The idea is part of the governmental plan to decentralize the National Library of Medicine. The aim of a Vision Information Center would be to apply the techniques of Medlars (Medical Literature Analysis and Retrieval System) to the field of ophthalmology and related science and to explore means for meeting the information explosion in the field of vision. Whether or not we have the competence and personnel for such an operation and, if so, whether or not it would be wise for us to undertake it is presently *sub judice.*

HONORS

Dr. Jin Kinoshita was signally honored this past year as recipient of the Friedenwald Award. This annual award of the Association for Research in Ophthalmology is the top prize for ophthalmic investigators. Dr. Kinoshita's remarks on acceptance of the Award tell such an interesting and significant story on the way of an investigator in ophthalmic research that we are enclosing the reprint with this Annual Report.

Dr. Cogan was honored by being awarded the Howe medals of the American Ophthalmological Society and the American Medical Association and by being the invited guest of the Japanese Ophthalmological Society. Honors are also due to Dr. Kuwabara who participated in the International Congress of Anatomists and to the other members of the Laboratory staff who were invited participants of less formal symposia and meetings.

We may further note with reflected pride that Dr. Herbert Kaufman was cited this past year as one of the country's Ten Outstanding Young Men by the United States Junior Chamber of Commerce. Dr. Kaufman is now Chief of Ophthalmology at the University of Florida but his remarkable discovery of IDU was made while he was a member of the Howe Laboratory and a resident at the Massachusetts Eye and Ear Infirmary.

BENEFACTIONS

The Howe Laboratory has a host of friends who include research support in their annual philanthropies. Others give to the Laboratory intermittently and a few have established memorial funds in the modern manner. The cumulative worth of these unrestricted contributions are immeasurable, both in terms of what free money can do and in the less tangible implications of support. We are most grateful.

We want to express especial gratitude this year for the beneficence of the late Carl E. Lilliestrand who, at the suggestion of his ophthalmologist, left a substantial part of his estate to the capital funds of the Laboratory. Funds such as these retain the name of the benefactor or the benefactor's designee and guarantee a continuing contribution to the cause of eye research. We know of no more humanitarian memorial.

We are grateful to the Lions Clubs of Massachusetts which contributed generously to the improvement of our electron microscopic facilities. We are grateful to Research to Prevent Blindness, Inc., Alcon Corporation, Bausch and Lomb, and Genradco who gave us unrestricted monies to launch pilot studies and to absorb unanticipated expenses which are an inevitable part of expanding research. We are grateful to The Seeing Eye, Inc. which contributed generously to Harvard's Department of Ophthalmology. We are grateful to the National Institutes of Health and the Atomic Energy Commission for their support of specific projects and of fellowships. And we have an especially warm feeling for the many individuals who have included the Howe Laboratory in their benefactions because they feel, as we do, that here the money will do the most good for the cause in which we are all interested.

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    Instrumentation in the field of ophthalmology
    Photographic recording of ophthalmic disease
    Control of intraocular pressure
    Projection of the human retina on the lateral geniculate nucleus
    Retinal metabolism
    Retinal microcirculation
    Ocular blood flow
    Corneal lipids
    Ocular hypersensitivity

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David G. Cogan, M.D.
Director

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FORM OF BEQUEST

The Howe Laboratory of Ophthalmology is an independent department of the Harvard Medical School and is jointly supported by a restricted endowment of Harvard University and by the Massachusetts Eye and Ear Infirmary.

For the information of those who may wish to contribute to this Laboratory, a form of bequest is here set forth:

I GIVE AND BEQUEATH TO THE HOWE LABORATORY OF

OPHTHALMOLOGY .... DOLLARS

TO BE APPLIED TO THE USES OF SAID LABORATORY.

Such bequests are managed by the Treasurer's Office of Harvard University, and the income is accredited to the Laboratory.